



THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

### **Expansion of the structure–activity relationships of BACE1 inhibitors by harnessing diverse building blocks prepared using a unified synthetic approach**

**Citation for published version:**

Mayol-Ilinà, J, Chow, S & Nelson, A 2019, 'Expansion of the structure–activity relationships of BACE1 inhibitors by harnessing diverse building blocks prepared using a unified synthetic approach', *Medchemcomm*. <https://doi.org/10.1039/C9MD00085B>

**Digital Object Identifier (DOI):**

[10.1039/C9MD00085B](https://doi.org/10.1039/C9MD00085B)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Peer reviewed version

**Published In:**

Medchemcomm

**General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

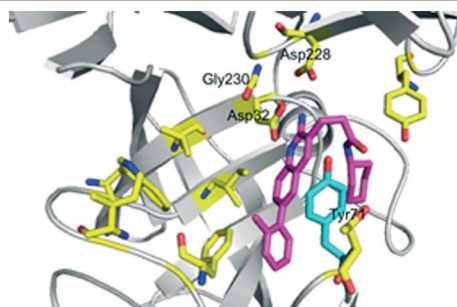
**Take down policy**

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



We have presented the Graphical Abstract text and image for your article below. This brief summary of your work will appear in the contents pages of the issue in which your article appears.

Q3



**Expansion of the structure–activity relationships of BACE1 inhibitors by harnessing diverse building blocks prepared using a unified synthetic approach**

Joan Mayol-Llinàs, Shiao Chow and Adam Nelson\*

The structural diversity of  $\beta$ -site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitors was expanded by harnessing diverse building blocks that had been prepared via a unified lead-oriented synthetic approach.

Please check this proof carefully. Our staff will not read it in detail after you have returned it.

Please send your corrections either as a copy of the proof PDF with electronic notes attached or as a list of corrections. **Do not edit the text within the PDF or send a revised manuscript** as we will not be able to apply your corrections. Corrections at this stage should be minor and not involve extensive changes.

**Proof corrections must be returned as a single set of corrections, approved by all co-authors. No further corrections can be made after you have submitted your proof corrections as we will publish your article online as soon as possible after they are received.**

Please ensure that:

- The spelling and format of all author names and affiliations are checked carefully. You can check how we have identified the authors' first and last names in the researcher information table on the next page. **Names will be indexed and cited as shown on the proof, so these must be correct.**
- Any funding bodies have been acknowledged appropriately and included both in the paper and in the funder information table on the next page.
- All of the editor's queries are answered.
- Any necessary attachments, such as updated images or ESI files, are provided.

Translation errors can occur during conversion to typesetting systems so you need to read the whole proof. In particular please check tables, equations, numerical data, figures and graphics, and references carefully.

Please return your **final** corrections, where possible within **48 hours** of receipt, by e-mail to: medchemcomm@rsc.org. If you require more time, please notify us by email.

## Funding information

Providing accurate funding information will enable us to help you comply with your funders' reporting mandates. Clear acknowledgement of funder support is an important consideration in funding evaluation and can increase your chances of securing funding in the future.

We work closely with Crossref to make your research discoverable through the Funding Data search tool (<http://search.crossref.org/funding>). Funding Data provides a reliable way to track the impact of the work that funders support. Accurate funder information will also help us (i) identify articles that are mandated to be deposited in **PubMed Central (PMC)** and deposit these on your behalf, and (ii) identify articles funded as part of the **CHORUS** initiative and display the Accepted Manuscript on our web site after an embargo period of 12 months.

Further information can be found on our webpage (<http://rsc.li/funding-info>).

### What we do with funding information

We have combined the information you gave us on submission with the information in your acknowledgements. This will help ensure the funding information is as complete as possible and matches funders listed in the Crossref Funder Registry.

If a funding organisation you included in your acknowledgements or on submission of your article is not currently listed in the registry it will not appear in the table on this page. We can only deposit data if funders are already listed in the Crossref Funder Registry, but we will pass all funding information on to Crossref so that additional funders can be included in future.

## Please check your funding information

The table below contains the information we will share with Crossref so that your article can be found *via* the Funding Data search tool. **Please check that the funder names and grant numbers in the table are correct and indicate if any changes are necessary to the Acknowledgements text.**

Q2

Funder name	Funder's main country of origin	Funder ID (for RSC use only)	Award/grant number
Engineering and Physical Sciences Research Council	United Kingdom	501100000266	EP/N025652/1
Takeda Pharmaceuticals North America	United States	100005570	NA
University of Leeds	United Kingdom	501100000777	Unassigned

## Researcher information

Please check that the researcher information in the table below is correct, including the spelling and formatting of all author names, and that the authors' first, middle and last names have been correctly identified. **Names will be indexed and cited as shown on the proof, so these must be correct.**

If any authors have ORCID or ResearcherID details that are not listed below, please provide these with your proof corrections. Please ensure that the ORCID and ResearcherID details listed below have been assigned to the correct author. Authors should have their own unique ORCID iD and should not use another researcher's, as errors will delay publication.

Please also update your account on our online [manuscript submission system](#) to add your ORCID details, which will then be automatically included in all future submissions. See [here](#) for step-by-step instructions and more information on author identifiers.

First (given) and middle name(s)	Last (family) name(s)	ResearcherID	ORCID
Joan	Mayol-Llinàs		0000-0002-9642-9201
Shiao	Chow		
Adam	Nelson		0000-0003-3886-363X

## Queries for the attention of the authors

Journal: **MedChemComm**

Paper: **c9md00085b**

Title: **Expansion of the structure–activity relationships of BACE1 inhibitors by harnessing diverse building blocks prepared using a unified synthetic approach**

For your information: You can cite this article before you receive notification of the page numbers by using the following format: (authors), Med. Chem. Commun., (year), DOI: 10.1039/c9md00085b.

Editor's queries are marked on your proof like this **Q1**, **Q2**, etc. and for your convenience line numbers are indicated like this 5, 10, 15, ...

Please ensure that all queries are answered when returning your proof corrections so that publication of your article is not delayed.

Query Reference	Query	Remarks
Q1	Please confirm that the spelling and format of all author names is correct. Names will be indexed and cited as shown on the proof, so these must be correct. No late corrections can be made.	
Q2	Funder details have been incorporated in the funder table using information provided in the article text. Please check that the funder information in the table is correct.	
Q3	Please check that the inserted Graphical Abstract text is suitable. Please ensure that the text fits between the two horizontal lines.	
Q4	Text has been provided for footnote a in Table 2, but there does not appear to be a corresponding citation in the table. Please indicate a suitable location for the footnote citation.	

# Expansion of the structure–activity relationships of BACE1 inhibitors by harnessing diverse building blocks prepared using a unified synthetic approach†

Cite this: DOI: 10.1039/c9md00085b

Q1

Received 8th February 2019,  
Accepted 14th March 2019

DOI: 10.1039/c9md00085b

rsc.li/medchemcomm

Joan Mayol-Llinàs,<sup>id</sup> Shiao Chow<sup>ab</sup> and Adam Nelson<sup>id</sup> <sup>†</sup> <sup>ab</sup>

The structural diversity of  $\beta$ -site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitors was expanded by harnessing diverse building blocks that had been prepared via a unified lead-oriented synthetic approach. It was shown that the lipophilic cyclohexylmethyl group within a known series of BACE1 inhibitors could be productively replaced with a range of alternative ring systems.

## Introduction

The exploration of chemical space, whilst controlling molecular properties at each stage of discovery, is an intrinsic challenge in medicinal chemistry.<sup>1</sup> Historically, chemical space has been explored unevenly and unsystematically,<sup>2</sup> which has limited the scaffold diversity of exemplified medicinal chemistry space.<sup>3</sup> Furthermore, discovery practices have driven medicinal chemists away from optimal property space, and have increased the focus on flatter and more lipophilic compounds.<sup>4</sup> Molecular weight (MW), lipophilicity and molecular complexity tend to increase during lead optimisation.<sup>5</sup> The challenge of controlling molecular properties in CNS discovery programmes is further heightened by the need to cross the blood–brain barrier.<sup>6</sup> To assist discovery, a multi-parameter optimisation (MPO) system for scoring CNS drug-likeness<sup>7</sup> has been developed that integrates scores for six key molecular properties.‡

Previously, we adapted<sup>8</sup> the CNS Lead MPO scoring system<sup>7</sup> to guide the development of a unified synthetic approach to diverse scaffolds that, on decoration, would provide high-quality starting points for CNS drug discovery.<sup>9</sup> Here, we demonstrate that these building blocks may be harnessed to expand the structural diversity of inhibitors of the CNS target BACE1. BACE1 is an aspartic protease that is responsible for the formation of amyloid  $\beta$  by sequential

cleavage of amyloid precursor protein (APP).<sup>10</sup> The amino-quinoline fragment **1**, which interacts with the two catalytic Asp residues, previously served as a starting point for fragment-based inhibitor discovery of BACE1 inhibitors.<sup>11</sup> Optimisation had initially involved the addition of an amide chain (to give **2**) bearing a lipophilic cyclohexylmethyl group. Successive addition of an *o*-tolyl group (to give **3**) and a methyl group (to give **4**) resulted, respectively, in  $\sim$ 900- and 9-fold increases in activity (Fig. 1).

## Results and discussion

Initially, we investigated the replacement of the lipophilic cyclohexylmethyl group in the inhibitor **2** with more highly functionalised substituents. Here, we exploited diverse building blocks that had been prepared using a unified synthetic approach developed to yield lead-like scaffolds for CNS drug discovery.<sup>9</sup> We initially prepared analogues of the amino-quinoline **2** in two steps from the ester<sup>11</sup> **5** (Table 1). In each case, the ester **5** was aminolysed<sup>12</sup> with the deprotected analogue of the appropriate racemic amine-containing building

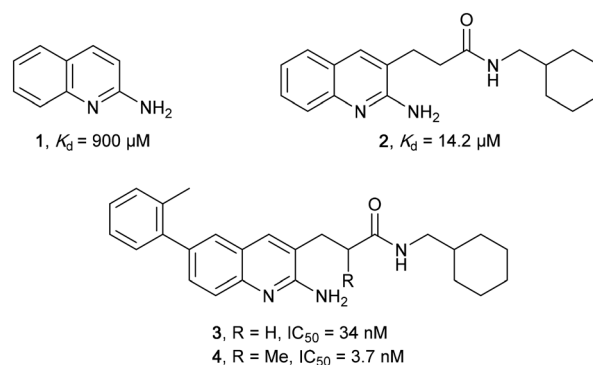


Fig. 1 Fragment-based discovery of a new class of BACE1 inhibitors (ref. 11).

<sup>a</sup> School of Chemistry, University of Leeds, Leeds, LS2 9JT, UK.

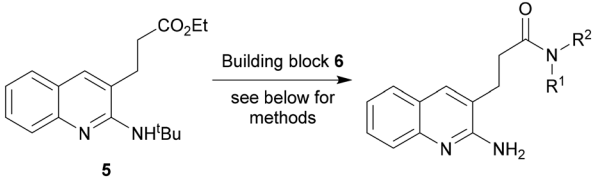
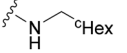
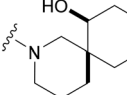
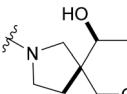
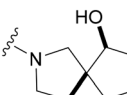
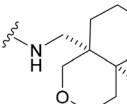
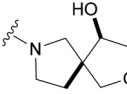
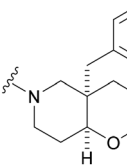
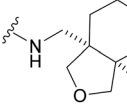
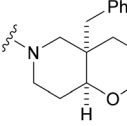
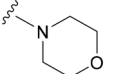
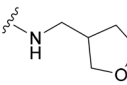
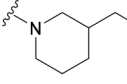
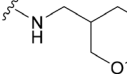
E-mail: a.s.nelson@leeds.ac.uk

<sup>b</sup> Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds, LS2 9JT, UK

† Electronic supplementary information (ESI) available: Synthetic procedures, compound characterisation, biochemical methods and computational approaches. See DOI: 10.1039/c9md00085b

‡ Scores for six molecular properties (MW; clogP; clogD<sub>7.4</sub>; pK<sub>a</sub>; polar surface area; number of hydrogen bond donors) contribute to the CNS drug-likeness score (maximum MPO score: 6) (ref. 7).

**Table 1** Synthesis and evaluation of potential BACE1 inhibitors

				
Building block	Product (Methods <sup>a</sup> )	NR <sup>1</sup> R <sup>2</sup>	Inhibition at 100 μM	IC <sub>50</sub> (μM) [pIC <sub>50</sub> ]
<b>6a</b>	<b>2</b> (A, 98%; B: 83%)		>95%	31 [4.51 ± 0.06]
<b>6b</b>	<b>7<sup>b</sup></b> (C, D, A, 21%; B, >99%)		<10%	—
<b>6c</b>	<b>8<sup>b</sup></b> (C, D, A, 60%; B, 93%)		<10%	—
<b>6d</b>	<b>9<sup>b</sup></b> (C, D, A, 75%; B, 32%)		>95%	55 [4.26 ± 0.01]
<b>6e</b>	<b>10<sup>b</sup></b> (D, A, 28%; B, 98%)		>95%	29 [4.54 ± 0.02]
<b>6f</b>	<b>11<sup>b</sup></b> (C, D, A, 72%; B, >99%)		<10%	—
<b>6g</b>	<b>12<sup>b</sup></b> (E, A, 20%; B, 99%)		<10%	—
<b>6h</b>	<b>13<sup>b</sup></b> (D, A, 31%; B, >99%)		<10%	—
<b>6i</b>	<b>14<sup>b</sup></b> (E, A, 23%; B, >99%)		67%	84 [4.07 ± 0.01]
<b>6j</b>	<b>15</b> (A, 56%; B, 93%)		<10%	—
<b>6k</b>	<b>16</b> (A, 90%; B, 47%)		<10%	—
<b>6l</b>	<b>17<sup>b</sup></b> (A, 37%; B, >99%)		<10%	—
<b>6m</b>	<b>18<sup>b</sup></b> (A, 43%; B, >99%)		<10%	—

<sup>a</sup> Methods: A: TBD, toluene, 75 °C; B: TFA, 75 °C; C: NaOMe, MeOH; D: TFA, CH<sub>2</sub>Cl<sub>2</sub>; E: H<sub>2</sub>, Pd/C, MeOH. TBD, triazabicyclodecene; TFA, trifluoroacetic acid. <sup>b</sup> Prepared as a racemate.



block 6 (see Fig. 2); TFA-induced deprotection then gave the corresponding free aminoquinoline.<sup>11</sup> For comparison, the known inhibitor 2 and its analogues 15–18 were also prepared from commercially-available amines.

Inhibition of BACE1 was initially assessed at 100  $\mu$ M using a fluorescence-quenching assay<sup>13</sup> based on the cleavage of a peptide substrate bearing a donor and a quencher at its termini. The dose-dependent activity of compounds that displayed significant inhibition at 100  $\mu$ M was subsequently determined. Three compounds, in which the cyclohexylmethyl group had been replaced, had broadly comparable activity to the parent aminoquinoline 2 (IC<sub>50</sub>: 31  $\mu$ M): the analogue 10 (IC<sub>50</sub>: 29  $\mu$ M) in which the secondary amide linkage had been retained, and the tertiary amides 9 (IC<sub>50</sub>: 55  $\mu$ M) and 14 (IC<sub>50</sub>: 84  $\mu$ M). The discovery of tertiary amide inhibitors was interesting because the secondary amide NH of 2 has been shown to form a key hydrogen bond interaction with a glycine residue in the BACE1 active site.<sup>11</sup> Notably, simplified analogues of the active compounds were inactive: for example, the secondary amide 18 (with a tetrahydropyran replacing the bicyclic ring system of 10) and the tertiary amide 17 (with a 3-benzyl piperidine replacing the benzyl-substituted bicyclic ring system of 14).

To provide some structural insights into these structure-activity relationships, the aminoquinoline 2 and both enantiomers of 10 and 14 were docked onto BACE1 using GOLD (Fig. 3 and ESI†).<sup>14</sup> The structure of BACE1 in complex with the aminoquinoline fragment 1 (PDB 2OHL) was used as a starting point for these *in silico* studies. Since alternative conformations of Tyr71 have been observed in BACE complexes with different aminoquinoline ligands,<sup>11</sup> this residue was allowed to be flexible.

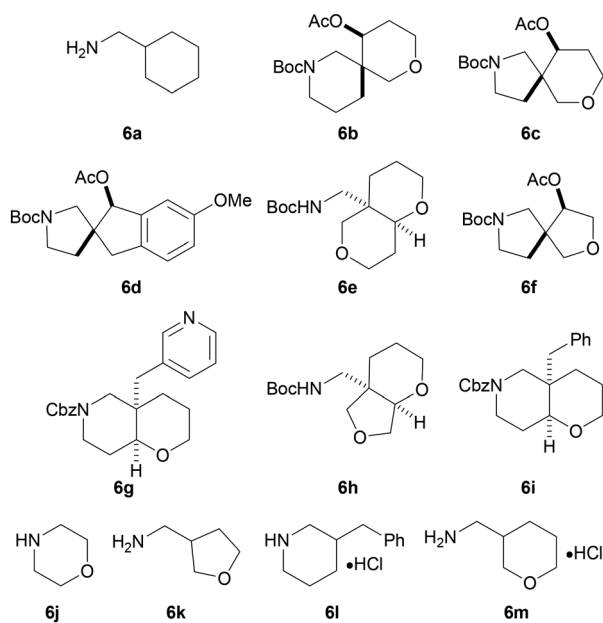


Fig. 2 Building blocks used in this study. The chiral building blocks were racemic.

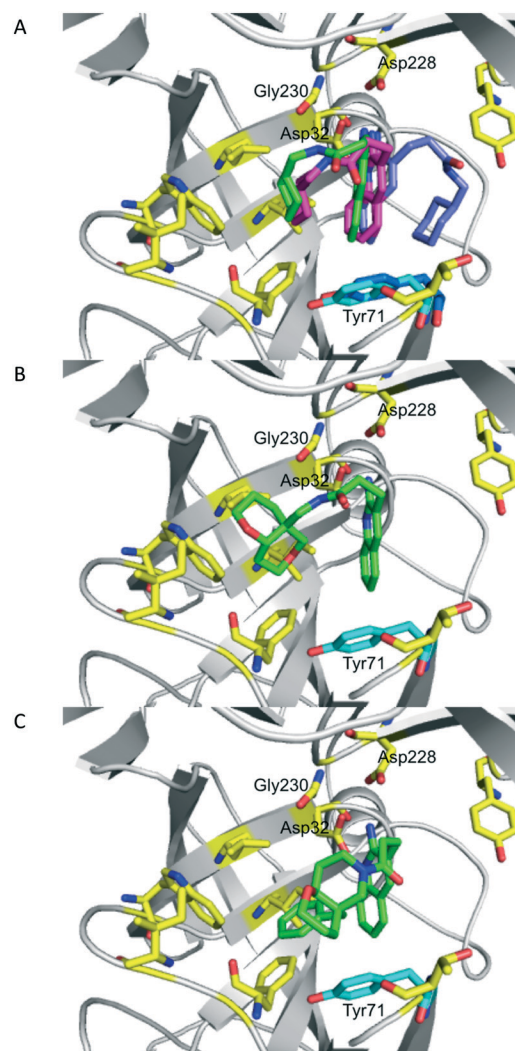
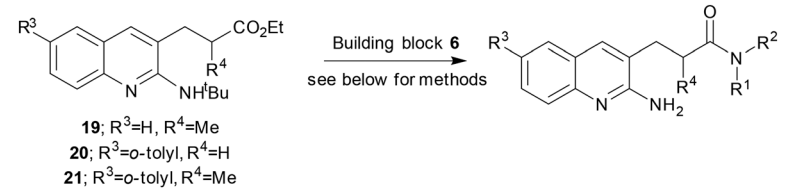


Fig. 3 Interaction of inhibitors with BACE1. Panel A: Docked pose of the aminoquinoline 2 superimposed on the alternative binding modes determined by X-ray crystallography (magenta and purple; PDB 3RU1). Panel B: Docked pose of (4aS,8aS)-10 (green). Panel C: Docked pose of (4aS,8aS)-14 (green).

Crystallographic studies had previously shown that the aminoquinoline 2 has two binding modes<sup>11</sup> in which its cyclohexyl substituent occupies either the P1 (magenta) or the P1' (purple) pocket (Fig. 3, Panel A). The docked pose of 2 (green) was similar to the binding mode in which the P1 pocket was targeted, with a similar orientation of Tyr71 (cyan) as the reported crystal structure (blue). Both enantiomers of 10 and 14 were also docked (see ESI†). For 10, the binding mode is predicted to be broadly similar to 2, with a hydrogen bond maintained between Gly230 and the secondary amide NH in the ligand (Panel B). The tertiary amides 9 and 14 lack the capacity to hydrogen bond with Gly230; however, the benzyl substituent of both enantiomers of 14 is predicted to bind in the same pocket as the cyclohexyl group of 2 (Panel C).

By analogy with the parent inhibitor 2 (Fig. 1), we investigated the addition of an *o*-tolyl group and/or a methyl group

**Table 2** Synthesis and evaluation of BACE1 inhibitors

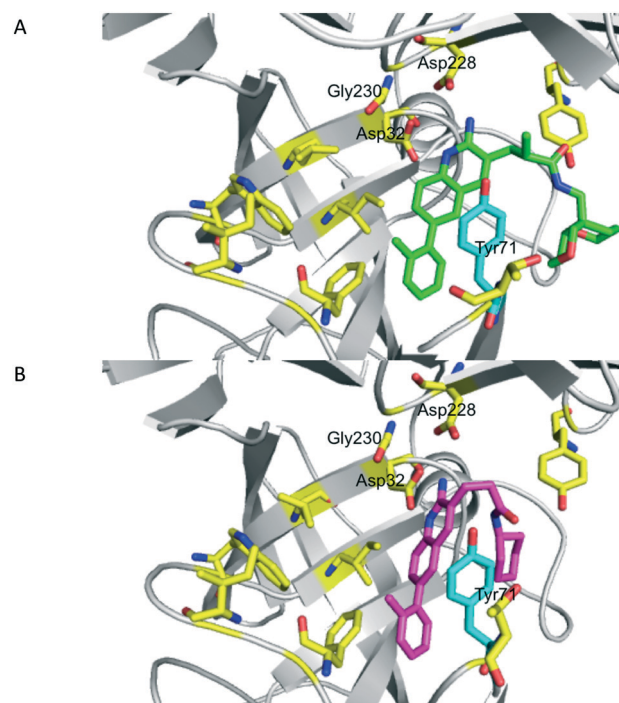
								
19; R <sup>3</sup> =H, R <sup>4</sup> =Me 20; R <sup>3</sup> = <i>o</i> -tolyl, R <sup>4</sup> =H 21; R <sup>3</sup> = <i>o</i> -tolyl, R <sup>4</sup> =Me								
Substrate	Building block	Product	Method (yield)	pIC <sub>50</sub>	IC <sub>50</sub> (μM)			
		NR <sup>1</sup> R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>				
19	6e	22	D, A, B (43% <sup>b</sup> )	4.48 ± 0.08	34	H	Me	
20	6e	23	D, A, B (60%)	7.11 ± 0.07	0.12	<i>o</i> -Tolyl	H	
21	6e	24	D, A, B (37% <sup>b</sup> )	7.51 ± 0.06	0.031	<i>o</i> -Tolyl	Me	
19	6d	25	C, D, A, B (29% <sup>b</sup> )	5.43 ± 0.02	3.7	H	Me	
20	6d	26	C, D, A, B (7%)	5.21 ± 0.06	6.1	<i>o</i> -Tolyl	H	
21	6d	27	C, D, A, B (16% <sup>b</sup> )	5.29 ± 0.06	5.1	<i>o</i> -Tolyl	Me	
19	6i	28	E, A, B (18% <sup>b</sup> )	4.47 ± 0.03	34	H	Me	
20	6i	29	E, A, B (39%)	5.50 ± 0.03	3.2	<i>o</i> -Tolyl	H	
21	6i	30	E, A, B (15% <sup>b</sup> )	5.57 ± 0.03	2.7	<i>o</i> -Tolyl	Me	

**Q4**<sup>a</sup> Methods: A: TBD, toluene, 75 °C; B: TFA, 75 °C; C: NaOMe, MeOH; D: TFA, CH<sub>2</sub>Cl<sub>2</sub>; E: H<sub>2</sub>, Pd/C, MeOH. <sup>b</sup> The use of two racemic reactants resulted in a 50 : 50 mixture of diastereomeric products. TBD, triazabicyclodecene; TFA, trifluoroacetic acid.

to the compounds **9**, **10** and **14** (Table 2). In each case, aminolysis of the appropriate ester (**19**, **20** or **21**) was followed TFA-induced deprotection; compounds prepared from the chiral esters **19** and **21** were obtained as 50 : 50 mixtures of racemic diastereomers. The dose-dependent activity of the resulting nine products was determined.

As with the secondary amide **2**, the addition of an *o*-tolyl group to **10** (IC<sub>50</sub>: 29 μM) to give **23** (IC<sub>50</sub>: 120 nM) resulted in a dramatic (~240-fold) improvement in activity. Furthermore, the subsequent addition of a methyl group to **23** (to give **24**; IC<sub>50</sub>: 31 nM) resulted in a further ~4-fold improvement in potency. The CNS drug-likeness scores<sup>7</sup> of these two compounds (3.47 for **23** and 3.00 for **24**) were broadly comparable with their cyclohexylmethyl analogues (3.20 for **3** and 3.10 for **4**). It is therefore possible to replace the cyclohexylmethyl substituent with a less lipophilic group (Δclog*P* for each pair: ~2.1) whilst maintaining both potency and CNS drug-likeness.

The inhibitor **24**, in which both an *o*-tolyl group and a methyl group have been incorporated, was docked onto BACE1 (see ESI† for all stereoisomers). The structure of BACE1 in complex with the aminoquinoline fragment **1** (PDB 2OHL) was used as a starting point, with alternative conformations of Tyr71 (cyan) allowed. The docked poses were substantially different to those of its unsubstituted analogue **10** (compare Fig. 4, Panel A and ESI† with Fig. 3, Panel B): the P1' pocket was now predicted to be targeted and the Tyr71 had a different orientation and formed a hydrogen bond with the secondary amide of the ligand. In the crystal structure<sup>11</sup>



**Fig. 4** Complexes of 2-amino-6-*o*-tolylquinoline inhibitors with BACE1 with Tyr71 highlighted (cyan). Panel A: Docked pose of a representative stereoisomer of the ligand **24** [with 2*R* configuration in linker and (4*aS*,8*aS*)-configured building block] Panel B: co-crystal structure of 3-(2-amino-6-*o*-tolylquinolin-3-yl)-*N*-cyclohexylpropanamide with BACE1 (PDB 3RTN).



of 3-(2-amino-6-*o*-tolylquinolin-3-yl)-*N*-cyclohexylpropanamide in complex with BACE1 (PDB 3RTN), the cyclohexyl substituent also targeted the P1' pocket and Tyr71 had a similar orientation (Fig. 4, Panel B).

With the tertiary amides **9** (IC<sub>50</sub>: 55 µM) and **14** (IC<sub>50</sub>: 84 µM), the addition of an *o*-tolyl group had a much less dramatic effect: ~8-fold (to give **26**; IC<sub>50</sub>: 6.1 µM) and ~14-fold (to give **29**; IC<sub>50</sub>: 3.2 µM) improvements in activity respectively were observed. In addition, the subsequent addition of a methyl groups to **26** and **29** (to give **27** and **30**) resulted in only modest improvements in activity.

## Conclusion

We have demonstrated that structurally-diverse, sp<sup>3</sup>-rich building blocks that were prepared using a unified lead-oriented approach can significantly enrich structure–activity relationships. In particular, we showed that the cyclohexylmethyl group in a series of known BACE1 inhibitors could be replaced productively with alternative structurally-diverse ring systems. Notably, the incorporation of simplified analogues of these alternative ring systems was not productive, and did not yield active BACE1 inhibitors. The availability of diverse building blocks *via* a lead-oriented synthetic approach therefore enabled the replacement of a lipophilic substituent with maintenance of both potency and CNS drug-likeness. The exploitation of diverse building blocks with controlled molecular properties within drug discovery programmes thus may significantly expand opportunities in lead discovery and optimisation.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We thank Takeda, the University of Leeds and EPSRC (EP/N025652/1) for funding, and Will Farnaby for helpful discussions.

## Notes and references

- 1 C. A. Lipinski, *Drug Discovery Today*, 2004, 1, 337.
- 2 (a) A. H. Lipkus, Q. Yuan, K. A. Lucas, S. A. Funk, W. F. Bartelt III, R. J. Schenck and A. J. Trippe, *J. Org. Chem.*, 2008, 73, 4443; (b) M. Garcia-Castro, S. Zimmermann, M. G. Sankar and K. Kumar, *Angew. Chem., Int. Ed.*, 2016, 55, 7586.
- 3 (a) G. W. Bemis and M. A. Murcko, *J. Med. Chem.*, 1996, 39, 2887; (b) S. R. Langdon, N. Brown and J. Blagg, *J. Chem. Inf. Model.*, 2011, 51, 2174.
- 4 (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, 52, 6752; (b) T. J. Ritchie and S. J. F. Macdonald, *Drug Discovery Today*, 2009, 14, 1011; (c) W. P. Walters, J. Green, J. R. Weiss and M. A. Murcko, *J. Med. Chem.*, 2011, 54, 6405.
- 5 (a) S. J. Teague, A. M. Davis, P. D. Leeson and T. Oprea, *Angew. Chem., Int. Ed.*, 1999, 38, 3743; (b) A. Nadin, C. Hattotuagama and I. Churcher, *Angew. Chem., Int. Ed.*, 2012, 51, 1114; (c) T. I. Oprea, A. M. Davis, S. J. Teague and P. D. Leeson, *J. Chem. Inf. Comput. Sci.*, 2001, 41, 1308.
- 6 A. K. Ghose, T. Herbertz, R. L. Hudkins, B. D. Dorsey and J. P. Mallamo, *ACS Chem. Neurosci.*, 2012, 3, 50.
- 7 T. T. Wager, X. Hou, P. R. Verhoest and A. Villalobos, *ACS Chem. Neurosci.*, 2010, 1, 435.
- 8 J. Mayol-Llinàs, A. Nelson, W. Farnaby and A. Ayscough, *Drug Discovery Today*, 2017, 22, 965.
- 9 J. Mayol-Llinàs, W. Farnaby and A. Nelson, *Chem. Commun.*, 2017, 53, 12345.
- 10 A. K. Ghosh and H. L. Osswald, *Chem. Soc. Rev.*, 2014, 43, 6765.
- 11 Y. Cheng, T. C. Judd, M. D. Bartberger, J. Brown, K. Chen, R. T. Freneau, Jr., D. Hickman, S. A. Hitchcock, B. Jordan, V. Li, P. Lopez, S. W. Louie, Y. Luo, K. Michelsen, T. Nixey, T. S. Powers, C. Rattan, E. A. Sickmier, D. J. St. Jean, Jr., R. C. Wahl, P. H. Wen and S. Wood, *J. Med. Chem.*, 2011, 54, 5836.
- 12 C. Sabot, K. A. Kumar, S. Meunier and C. Mioskowski, *Tetrahedron Lett.*, 2007, 48, 3863.
- 13 T. Zauner, R. Berger-Hoffmann, K. Müller, R. Hoffmann and T. Zuchner, *Anal. Chem.*, 2011, 83, 7356.
- 14 G. Jones, P. Willett, R. C. Glen, A. R. Leach and R. Taylor, *J. Mol. Biol.*, 1997, 267, 727.